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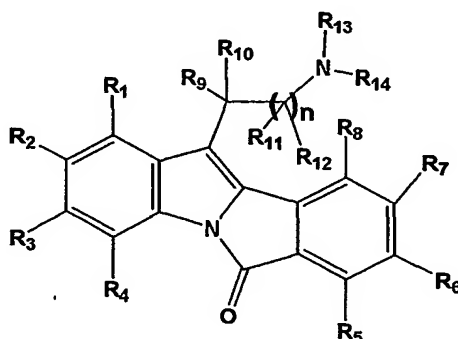
(54) Title: NOVEL TETRACYCLIC ARYLCARBONYL INDOLES HAVING SEROTONIN RECEPTOR AFFINITY USEFUL AS THERAPEUTIC AGENTS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: The present invention relates to novel tetracyclic arylcarbonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them. This invention particularly relates to novel tetracyclic arylcarbonyl indoles of the general formula (I), their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them. This invention also relates to process/es for preparing such compound/s of general formula (I), composition/s containing effective amount/s of such a compound and the use of such a compound/composition in therapy

Novel tetracyclic arylcarbonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them

Field of Invention:

The present invention relates to novel tetracyclic arylcarbonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.



General formula (I)

The present invention also relates to the process for preparing the compounds of general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

The compounds of the general formula (I) of this invention are 5-HT (Serotonin) ligands e.g. agonists or antagonists. The compounds of the general formula (I) of this invention, by the virtue of there chemical characteristic, could either independently or simultaneously modulate the melatonin receptor i.e. either they are melatoninerigic ligands e.g. agonists or antagonists, or they interact with both 5-HT as well as melatonin receptor.

Thus, compounds of general formula (I) of this invention are useful for treating diseases wherein activity of either 5-HT (Serotonin) and/or melatonin is modulated to obtain the desired effect. Specifically, the compounds of this invention are useful in the treatment and / or prophylaxis of psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, anxiety, migraine headache, depression, drug addiction, convulsive disorders, personality disorders, hypertension, autism, post-traumatic stress syndrome, alcoholism, panic attacks, obsessive-compulsive disorders, chronobiological abnormalities, circadian rhythms, anxiolytic, osteoporosis, ischemic stroke, lower the risk of

SIDS in young infants with low endogenous melatonin levels, reproduction, glaucoma and sleep disorders.

The compounds of general formula (I) of this invention are also useful to treat psychotic, affective, vegetative and psychomotor symptoms of schizophrenia and the extrapyramidal motor side effects of other antipsychotic drugs.

The compounds of general formula (I) of this invention are also useful to treat neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting. The compounds of general formula (I) of this invention are also useful in modulation of eating behavior and thus are useful in reducing the morbidity and mortality associated with excess weight.

Background of the Invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic and the serotonergic neurotransmitter systems. Serotonin has been implicated in a number of diseases and conditions, which originate in the central nervous system. these include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia and other bodily states. (References: Fuller, R. W., Drugs Acting on Serotonergic Neuronal Systems, Biology of Serotonergic Transmission, John Wiley & Sons Ltd. (1982), 221-247; Boullin D. J., Serotonin in Mental abnormalities (1978), 1, 316; Barchas J. et. al., Serotonin and Behavior (1973)). Serotonin also plays an important role in the peripheral systems, such as the gastrointestinal system, where it has been found to mediate a variety of contractile, secretory and electrophysiologic effects.

Due to the broad distribution of serotonin within the body, there is lot of interest and use, in the drugs that affect serotonergic systems. Particularly, preferred are the compounds which have receptor specific agonism and/or antagonism for the treatment of a wide range of disorders, including anxiety, depression, hypertension, migraine, obesity, compulsive disorders, schizophrenia, autism, neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea and chemotherapy-induced vomiting (References: Gershon M. D. et. al., The peripheral actions of 5-Hydroxytryptamine (1989), 246; Saxena P. R. et. al., Journal of Cardiovascular Pharmacology (1990), supplement 7, 15).

The major classes of serotonin receptors (5-HT₁₋₇) contain fourteen to eighteen separate receptors that have been formally classified (References: Glennon et al, Neuroscience and Behavioral Reviews (1990), 14, 35 and Hoyer D. et al, Pharmacol. Rev. (1994), 46, 157-203). Recently discovered information regarding sub-type identity, distribution, structure and function suggests that it is possible to identify novel, sub-type specific agents having improved therapeutic profiles with lesser side effects. The 5-HT₆ receptor was identified in 1993 (References: Monsma et al, Mol. Pharmacol. (1993), 43, 320-

327 and Ruat M. et al, Biochem. Biophys. Res. Com. (1993), 193, 269-276). Several antidepressants and atypical antipsychotics bind to the 5-HT₆ receptor with high affinity and this binding may be a factor in their profile of activities (References: Roth et al, J. Pharm. Exp. Therapeut. (1994), 268, 1403-1410; Sleight et al, Exp. Opin. Ther. Patents (1998), 8, 1217-1224; Bourson et al, Brit. J. Pharmacol. (1998), 125, 1562-1566; Boess et al, Mol. Pharmacol., 1998, 54, 577-583; Sleight et al, Brit. J. Pharmacol. (1998), 124, 556-562). In addition, 5-HT₆ receptor has been linked to generalized stress and anxiety states (Reference: Yoshioka et al, Life Sciences (1998), 17/18, 1473-1477). Together these studies and observations suggest that compounds that antagonize the 5-HT₆ receptor will be useful in treating various disorders of the central nervous system.

There is very strong evidence that melatonin is important for the regulation of a variety of neural and endocrine functions, especially those that exhibit circadian and circannual rhythmicity. Great interest therefore lies in the possibility of making available to the clinician melatonin analogues that are metabolically more stable and have an agonist or antagonist character and of which the therapeutic effect may be expected to be superior to that of the hormone itself. PCT patent application gives extensive literature on studies with melatonin and potential therapeutic application of various ligands reported till date.

Those various effects are exerted via the intermediary of specific melatonin receptors. Molecular biology studies have demonstrated the existence of a number of receptor sub-types that are capable of binding that hormone (Trends Pharmacol. Sci., 1995, 16, p. 50; WO 97 04094). Melatonin acts on the CNS to affect neural mechanisms through receptors located in the brain. Additionally, a number of studies indicate the existence of direct effects of melatonin in peripheral organs via peripheral melatonin receptors. Melatonin receptors are present in the heart, lungs, prostate gland, gonads, white blood cells, retina, pituitary, thyroid, kidney, gut and blood vessels (Withyachumnarnkul et al., Life Sci, 12 65, 1986). Three melatonin receptor subtypes have been identified so far MT-1, MT-2 and Mel 1c (Barreft et al., Biol. Signals Recept., 1999, 8: 6-14).

There is evidence suggesting both melatonin agonists and antagonists would be of potential therapeutic use for a variety of maladies and conditions. PCT application WO 00/72815, discuss in depth applications and use of such compounds and details of which are incorporated herein by reference. Also U. S. patent 6465660 and U. S. patent application publication number US 2003/0105087 discuss some tricyclic indole and tricyclic azaindole derivatives having very valuable pharmacological characteristics in respect of melatoninergetic receptors.

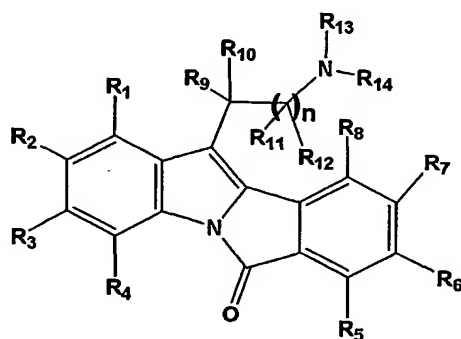
U. S. patent 4,839,377 and U. S. patent 4,855,314 refer to 5-substituted 3-aminoalkyl indoles. The compounds are said to be useful for the treatment of migraine.

International Patent Publication WO 94/06769, refers to 2-substituted-4-piperazine-benzothiophene derivatives that are serotonin 5-HT_{1A} and 5-HT_{1D} receptor agents useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

Summary of the Invention:

The present invention relates to novel tetracyclic arylcarbonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

More particularly, the present invention relates to novel tetracyclic arylcarbonyl indoles of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in medicine.



General formula (I)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its

derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R₁ and R₂ or R₂ and R₃ or R₃ and R₄ or R₅ and R₆ or R₆ and R₇ or R₇ and R₈ together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R₉ and R₁₀ or R₁₁ and R₁₂ together represent double bond attached to "Oxygen" or "Sulfur"; or R₉ and R₁₀ or R₁₁ and R₁₂ together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R₁₃ and R₁₄ may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₂-C₁₂)alkanoyl (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclalkyl; optionally R₁₃ and R₁₄ along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Partial list of such compounds of general formula (I) is as follows:

- 11-(2-N,N-Dimethylaminoethyl)isoindolo[2,1-a]indol-6-one;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one hydrochloride salt;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one maleic acid salt;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one D,L-malic acid salt;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one oxalate salt;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one citrate salt;
- 11-[(2-N-cyclopropyl-N-methylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
- 11-[2-N-cyclopropylethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
- 2-Bromo-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
- 2-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
- 4-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-methylisoindolo[2,1-a]indol-6-one;
- 11-[(2-N,N-Dimethylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
- 11-[(2-N,N-Diacetylaminomethyl)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;

- 11-[(2-N-Acetylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
 11-[(2-N,N-Dimethylamino)ethyl]-4-methoxyisoindolo[2,1-a]indol-6-one;
 11-[(2-N,N-Dimethylamino)ethyl]-4-trifluoromethylisoindolo[2,1-a]indol-6-one;
 11-[(2-N,N-Dimethylamino)ethyl]-4-ethylisoindolo[2,1-a]indol-6-one;
 5 11-[(2-N,N-Dimethylamino)ethyl]-2,4-difluoroisoindolo[2,1-a]indol-6-one;
 2,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
 3,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
 1,2,4-Trichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
 11-[(2-N,N-Dimethylamino)ethyl]-2,4-dimethylisoindolo[2,1-a]indol-6-one;
 10 11-[(2-N,N-Dimethylamino)ethyl]-3,4-dimethylisoindolo[2,1-a]indol-6-one;
 1-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N,N-diacetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N-acetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N-acetylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
 15 3-Chloro-11-[(2-N-acetylamino)ethyl]-2-sulfoamidoisoindolo[2,1-a]indol-6-one;
 3-Iodo-11-[(2-N-acetylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 11-[(2-N,N-Dimethylamino)propyl]-4-methylisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N-methylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 20 3-Chloro-11-[(2-N-methyl-N-acetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N-methylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
 3-Chloro-11-[(2-N-methylamino)ethyl]-2-sulfoamidoisoindolo[2,1-a]indol-6-one;
 3-Iodo-11-[(2-N-methylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
 2-Bromo-11-[(2-morpholin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one;
 25 2-Bromo-11-[2-(4-methylpiperazin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one;
 and its stereoisomers, its N-oxides, its polymorphs, its pharmaceutically acceptable salts
 and solvates.

The present invention also envisages some useful bio-active metabolites of the compounds of general formula (I).

- 30 The compounds of general formula (I) of this invention are useful in the treatment and/ or prophylaxis of a condition wherein modulation of 5-HT and or Melatonin activity is desired.

- 35 The present invention provides for use of the compounds of general formula (I) according to above, for the manufacture of the medicaments for the potential use in the treatment and/ or prophylaxis of certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD

(Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, chronobiological abnormalities, circadian rhythms, anxiolytic, osteoporosis, ischemic stroke, lower the risk of SIDS in young infants with low endogenous melatonin levels, reproduction, glaucoma, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and / or head injury such as hydrocephalus. Compounds of the invention are further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The compounds of the invention are also expected to be of use in the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.

The compounds of the invention are also expected to be of use in the modulation of eating behavior and these compounds can also be used to reduce morbidity and mortality associated with the excess weight.

The present invention provides a method for the treatment of a human or a animal subject suffering from certain CNS disorders such as, anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders e.g. Alzheimer's disease and age-related cognitive decline, ADHD (Attention Deficient Hyperactivity Disorder), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, panic attacks, chronobiological abnormalities, circadian rhythms, anxiolytic, osteoporosis, ischemic stroke, lower the risk of SIDS in young infants with low endogenous melatonin levels, reproduction, glaucoma, sleep disorders (including disturbances of Circadian rhythm) and also disorders associated with spinal trauma and /or head injury such as hydrocephalus. Compounds of the invention are further expected to be of use in the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.

The present invention also provides a method for modulating 5-HT and/ or Melatonin receptor function desired in certain cases.

The present invention also includes a isotopically-labelled compounds, which are identical to those defined in the general formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number found usually in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen,

oxygen, phosphorus, fluorine, chlorine, iodine, bromine and mTecnitium, exemplified by ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{18}F , $^{99\text{m}}\text{Tc}$, ^{31}P , S , ^{123}I and ^{125}I . Compounds of present invention and pharmaceutically acceptable salts and prodrugs of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention.

Isotopically labelled compounds of the present invention are useful in drug and/or substrate tissue distribution and target occupancy assays. For example, isotopically labelled compounds are particularly useful in SPECT (single photon emission computed tomography) and in PET (positron emission tomography).

An effective amount of a compound of general formula (I) or its salt is used for producing medicaments of the present invention, along with conventional pharmaceutical auxiliaries, carriers and additives.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

- a. a pharmaceutically acceptable carrier
- b. a compound of general formula (I) as defined above, and
- c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

- a. a pharmaceutically acceptable carrier
- b. a compound of general formula (I) as defined above, and
- c. a 5-HT re-uptake inhibitor, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a 5-HT re-uptake inhibitor), is such that the combination is effective in treating such a condition.

The present invention also relates to a pharmaceutical composition for treating and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

- a. a pharmaceutically acceptable carrier
- b. a compound of general formula (I) as defined above, and
- c. either of serotonergic or melatonergic ligand, or its pharmaceutically acceptable salt;

wherein the amounts of each active compound (a compound of general formula (I) and a serotonergic or melatonergic ligand), is such that the combination is effective in treating such a condition.

5 The present invention also relates to a method of treatment and/or prophylaxis of disorders, a condition wherein modulation of 5-HT and/or melatonin is desired in a mammal, comprising:

- a. a pharmaceutically acceptable carrier
- b. a compound of general formula (I) as defined above, and
- c. either of a serotonergic or melatonergic ligand, or its pharmaceutically acceptable
10 salt;

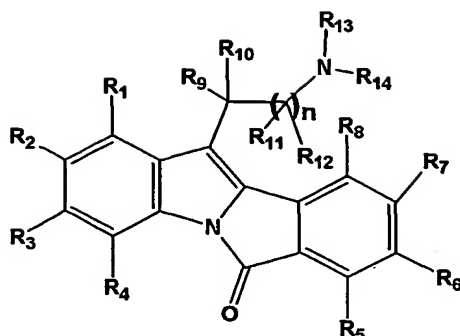
wherein the amounts of each active compound (a compound of general formula (I) and a serotonergic or melatonergic ligand), is such that the combination is effective in treating such a condition.

15 The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their geometric forms, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutical compositions containing them.

Detailed description of the invention:

20 The present invention relates to novel tetracyclic arylcarbonyl indoles, their derivatives, their analogues, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them.

25 More particularly, the present invention relates to novel tetracyclic arylcarbonyl indoles of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, novel intermediates described herein and pharmaceutically acceptable compositions containing them and use of these compounds in
30 medicine.



General formula (I)

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12}) alkoxy, cyclo (C_3-C_7) alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_2-C_{12}) alkanoyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl,

bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

5 "n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

Suitable groups represented by R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} may be a halogen atom such as fluorine, chlorine, bromine or iodine; perhaloalkyl particularly perhalo(C_1 - C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, 10 trifluoroethyl, fluoroethyl, difluoroethyl and the like; substituted or unsubstituted (C_1 - C_{12})alkyl group, linear or branched (C_1 - C_8)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, iso-hexyl, heptyl, octyl and the like; substituted or unsubstituted (C_2 - C_{12})alkenyl group such as ethylene, n-propylene pentenyl, hexenyl, heptynyl, heptadienyl and the like; (C_2 - C_{12})alkynyl substituted or unsubstituted (C_2 - 15 C_{12})alkynyl group such as acetylene and the like; cyclo(C_3 - C_7)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, the cycloalkyl group may be substituted; cyclo(C_3 - C_7)alkenyl group such as cyclopentenyl, cyclohexenyl, cycloheptynyl, cycloheptadienyl, cycloheptatrienyl and the like, the cycloalkenyl group may be substituted; (C_1 - C_{12})alkoxy, especially, (C_1 - C_6)alkoxy group such as methoxy, ethoxy, propyloxy, 20 butyloxy, iso-propyloxy and the like, which may be substituted; cyclo(C_3 - C_7) alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the 25 substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, $Hal-C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocycl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocycl group may be substituted; heteroaryl group such as pyridyl, thienyl, 30 furyl, pyrrolyl, oxazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heterocyclo(C_1 - C_6)alkyl, such as pyrrolidinylalkyl, piperidinylalkyl, morpholinylalkyl, thiomorpholinylalkyl, oxazolylalkyl and the like, the heterocyclo(C_1 - C_6)alkyl group may be substituted; heteroaralkyl group such as furanylmethyl, pyridinylmethyl, oxazolylmethyl, oxazolylethyl and the like, the heteroaralkyl 35 group may be substituted; heteroaryloxy, heteroaralkoxy, heterocycloalkoxy, wherein heteroaryl, heteroaralkyl, heterocycloalkyl and heterocyclalkyl moieties are as defined earlier and may be substituted; acyl groups such as acetyl, propionyl or benzoyl, the acyl

group may be substituted; acyloxy group such as CH_3COO , $\text{CH}_3\text{CH}_2\text{COO}$, $\text{C}_6\text{H}_5\text{COO}$ and the like which may optionally be substituted, acylamino group such as CH_3CONH , $\text{CH}_3\text{CH}_2\text{CONH}$, $\text{C}_3\text{H}_7\text{CONH}$, $\text{C}_6\text{H}_5\text{CONH}$ which may be substituted, (C₁-C₆)monoalkylamino group such as CH_3NH , $\text{C}_2\text{H}_5\text{NH}$, $\text{C}_3\text{H}_7\text{NH}$, $\text{C}_6\text{H}_{13}\text{NH}$ and the like, which may be substituted,

5 (C₁-C₆)dialkylamino group such as $\text{N}(\text{CH}_3)_2$, $\text{CH}_3(\text{C}_2\text{H}_5)\text{N}$ and the like, which may be substituted; arylamino group such as $\text{C}_6\text{H}_5\text{NH}$, $\text{CH}_3(\text{C}_6\text{H}_5)\text{N}$, $\text{C}_6\text{H}_4(\text{CH}_3)\text{NH}$, $\text{NH}-\text{C}_6\text{H}_4-\text{Hal}$ and the like, which may be substituted; arylalkylamino group such as $\text{C}_6\text{H}_5\text{CH}_2\text{NH}$, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}$, $\text{C}_6\text{H}_5\text{CH}_2\text{NCH}_3$ and the like, which may be substituted; hydroxy(C₁-C₆)alkyl which may be substituted, amino(C₁-C₆)alkyl which may be substituted; mono(C₁-

10 C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl group which may be substituted, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; aryloxyalkyl group such as $\text{C}_6\text{H}_5\text{OCH}_2$, $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2$, $\text{C}_6\text{H}_5\text{CH}_2\text{OCH}_2\text{CH}_2$ and the like, which may be substituted; (C₁-C₆)alkylthio,

15 thio(C₁-C₆)alkyl which may be substituted, alkoxycarbonylamino group such as $\text{C}_2\text{H}_5\text{OCONH}$, CH_3OCONH and the like which may be substituted; aryloxycarbonylamino group as $\text{C}_6\text{H}_5\text{OCONH}$, $\text{C}_6\text{H}_5\text{OCONCH}_3$, $\text{C}_6\text{H}_5\text{OCONC}_2\text{H}_5$, $\text{C}_6\text{H}_4\text{CH}_3\text{OCONH}$, $\text{C}_6\text{H}_4(\text{OCH}_3)\text{OCONH}$ and the like which may be substituted; aralkoxycarbonylamino group such $\text{C}_6\text{H}_5\text{CH}_2\text{OCONH}$, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OCONH}$, $\text{C}_6\text{H}_5\text{CH}_2\text{OCON}(\text{CH}_3)$, $\text{C}_6\text{H}_5\text{CH}_2\text{OCON}(\text{C}_2\text{H}_5)$,

20 $\text{C}_6\text{H}_4\text{CH}_3\text{CH}_2\text{OCONH}$, $\text{C}_6\text{H}_4\text{OCH}_3\text{CH}_2\text{OCONH}$ and the like, which may be substituted; aminocarbonylamino group; (C₁-C₆)alkylaminocarbonylamino group, di(C₁-C₆)alkylaminocarbonylamino group; (C₁-C₆)alkylamidino group, (C₁-C₆)alkylguanidino, di(C₁-C₆)alkylguanidino groups, hydrazino and hydroxylamino groups; carboxylic acid or its derivatives such as amides, like CONH_2 , alkylaminocarbonyl like CH_3NHCO , $(\text{CH}_3)_2\text{NCO}$,

25 $\text{C}_2\text{H}_5\text{NHCO}$, $(\text{C}_2\text{H}_5)_2\text{NCO}$, arylaminocarbonyl like PhNHCO , NaphthylNHCO and the like, aralkylaminocarbonyl such as PhCH_2NHCO , $\text{PhCH}_2\text{CH}_2\text{NHCO}$ and the like, heteroarylaminocarbonyl and heteroaralkylamino carbonyl groups where the heteroaryl groups are as defined earlier, heterocyclaminocarbonyl where the heterocycl group is as defined earlier, carboxylic acid derivatives such as esters, wherein the ester moieties are

30 alkoxy carbonyl groups such as unsubstituted or substituted phenoxy carbonyl, naphthyloxy carbonyl and the like; aralkoxy carbonyl group such as benzyloxy carbonyl, phenethyloxy carbonyl, naphthylmethoxy carbonyl and the like, heteroaryloxy carbonyl, heteroaralkoxy carbonyl, wherein the heteroaryl group is as defined earlier, heterocycloxy carbonyl where heterocycle is as defined earlier and these carboxylic acid

35 derivatives may be substituted; sulfonic acid or its derivatives such as SO_2NH_2 , SO_2NHCH_3 , $\text{SO}_2\text{N}(\text{CH}_3)_2$, SO_2NHCF_3 , $\text{SO}_2\text{NHCO}(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{SO}_2\text{NHCOaryl}$ where the aryl group is as

the solvent of crystallization, inherent in the solvent preparation or crystallization, or adventitious to such solvent. Such solvates are within the scope of this invention.

The invention also encompasses the pharmaceutically acceptable prodrugs of the compounds of the formula (I). A prodrug is a drug which has been chemically modified and may be biologically in-active at the site of action, but which may be degraded or modified by one or more enzymatic or other in-vivo processes to the parent form. This prodrug should have a different pharmacokinetic profile than the parent, enabling easier absorption across the mucosal epithelium, better salt formation, or solubility, and/or improved systemic stability (an increase in the plasma half-life, for example). Typically, such chemical modifications include the following:

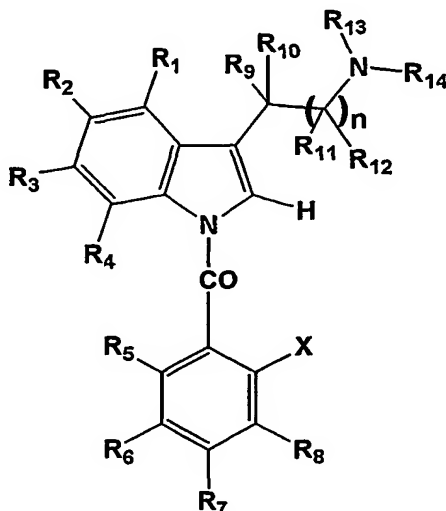
1. ester or amide derivatives which may be cleaved by esterases or lipases;
2. peptides which may be recognized by specific or non-specific proteases; or
3. derivatives that accumulate at a site of action through membrane selection of a prodrug from or a modified prodrug form; or any combination of 1 to 3, above.

Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in H. Bundgard, Design of prodrugs, (1985).

Compounds of general formula (I) can be prepared by any of the methods described below. The present invention also provides processes for preparing compounds of general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their geometric forms, their polymorphs, their pharmaceutically acceptable salts and their pharmaceutically acceptable solvates, novel intermediates described herein, where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and "n" are as defined previously can be prepared by any of the methods described below:

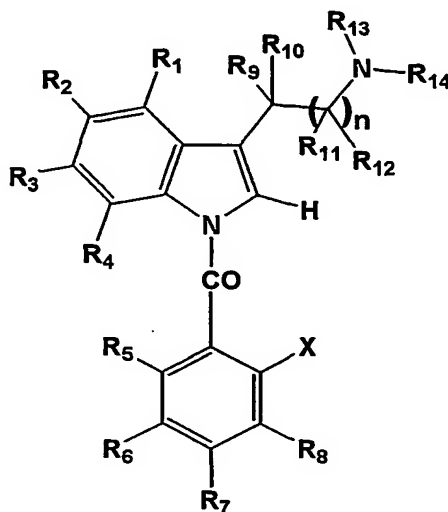
Scheme - 1 :

Compounds of general formula (I), may be prepared by cyclizing a novel intermediate of formula (II) given below,



Compounds of general formula (I), may be prepared from another compound of formula (I) containing -C(=O) group/s in the side chain, by known methods of reduction to the corresponding -C(OH,H) or -C(H,H) compound; and thereafter if desired or necessary carrying out steps (i), (ii) and/or (iii) as described above.

- 5 Novel intermediates of general formula (II), their stereoisomers and their salts, represented as given below,



(II)

wherein X is halogen such chloro, bromo or iodo.

- 10 $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}$ and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12}) alkoxy, cyclo (C_3-C_7) alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxylalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxy carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and

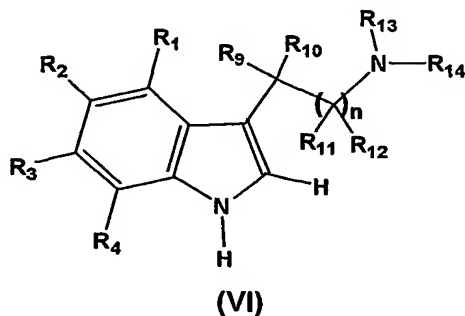
combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_2-C_{12}) alkanoyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above.

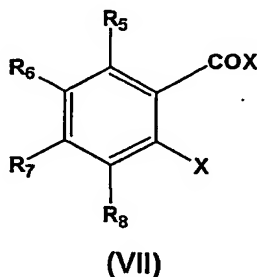
"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

The present invention also provides processes for preparing the novel intermediate represented by the general formula (II).

Route - 1 : Compounds of general formula (II), may be prepared by reacting a compound of formula (VI) given below,



where R_1 , R_2 , R_3 , R_4 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} and R_{14} are as defined in relation to formula (I); with a compound of formula (VII)



where R_5 , R_6 , R_7 and R_8 are as defined in relation to formula (I) and X is a halogen,

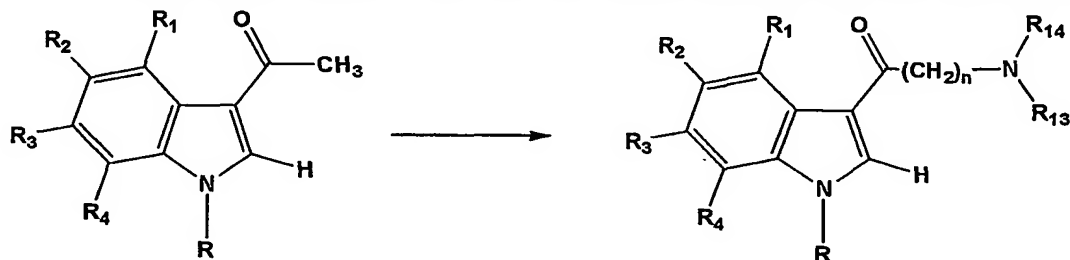
preferably chloro, bromo or iodo.

This reaction may be carried out in the presence of solvents such as THF, DMF, DMSO, DME, acetone and the like and preferably using either acetone or DMF. The inert atmosphere may be maintained by using inert gases such as N₂, Ar or He. The reaction may be affected in the presence of a base such as K₂CO₃, Na₂CO₃, NaH, KH or mixtures thereof. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours. (Reference: Bio Org. Med Chem. 2000. 10, 2295-2299).

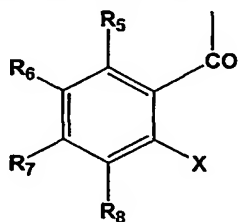
Preferably the substituents selected for the compounds of formula (VI) and (VII) are either not affected by the reaction conditions or else the sensitive groups are protected using suitable groups.

Compounds of formula (VI) are commercially available, or they may be prepared by conventional methods or by modification, using known processes, of commercially available compounds of formula (VI). PCT patent application WO 02/078693 also provides methods to prepare variously substituted indoles as well as tryptamines and is incorporated herein by reference.

Route - 2 : Compounds of general formula (II) may be prepared by the following route



wherein R₁, R₂, R₃, R₄, R₁₁, R₁₂, R₁₃, R₁₄ and n (=2) are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

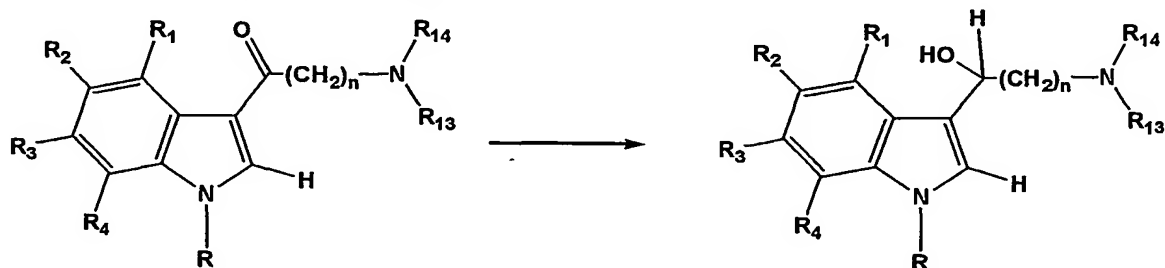


wherein X is halogen such as chloro, bromo or iodo; R₅, R₆, R₇ and R₈ are as defined earlier; in presence of amine hydrochloride and formaldehyde.

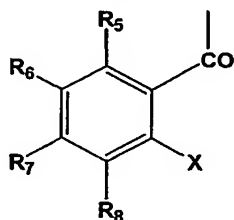
The above reaction is preferably carried out at a temperature of 50 °C to 150 °C. The formaldehyde can be in the form of as aqueous solution i.e. 40 % formalin solution, or a polymeric form of formaldehyde such as paraformaldehyde or trioxymethylene. When such

polymeric forms are used, a molar excess of mineral acid, for example hydrochloric acid, is added to regenerate the free aldehyde from the polymer. The reaction is preferably carried in an organic solvent inert to the conditions of the reaction, such as methanol, ethanol or 3-methylbutanol and the like or a mixture thereof. The inert atmosphere may be maintained by using inert gases, such as N₂, Ar or He. The reaction temperature may range from 20 °C to 150 °C based on the choice of solvent and preferably at a temperature in the range from 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

- 10 Route - 3 : Compounds of general formula (II) may be prepared reducing another compound of formula (I) as follows,

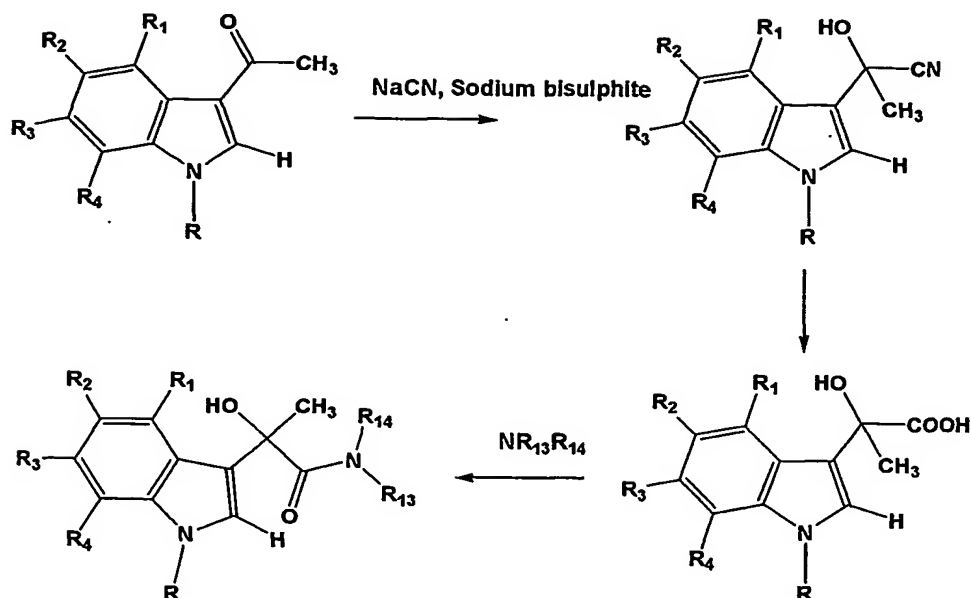


wherein R₁, R₂, R₃, R₄, R₁₁, R₁₂, R₁₃, R₁₄ and n (=2) are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

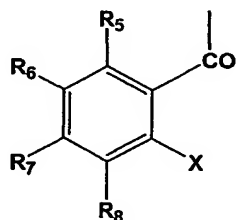


wherein X is halogen such as chloro, bromo or iodo; R₅, R₆, R₇ and R₈ are as defined earlier; by use of known various methods of either catalytic (for example, palladium/carbon), chemical (for example, sodium borohydride) or enzymatic reduction.

- 20 Route - 4 : Compounds of general formula (II) may be prepared by the following route



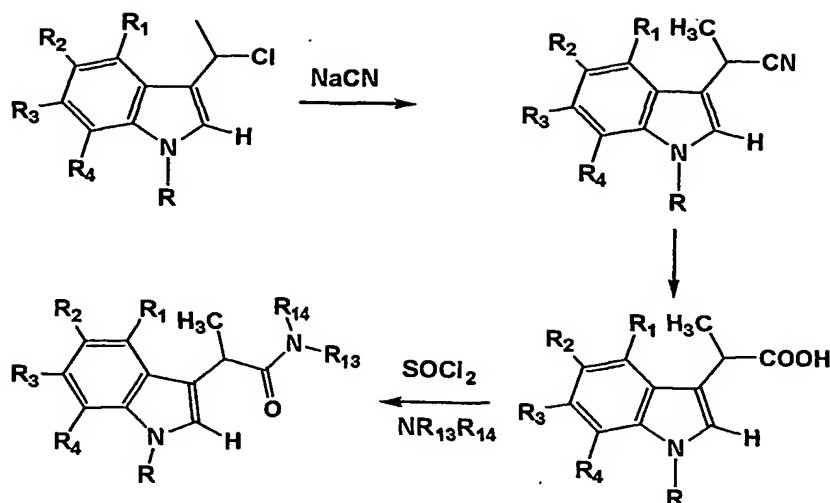
wherein $R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14}$ and n are as defined in relation to formula (I); R represents either of hydrogen or a group such as,



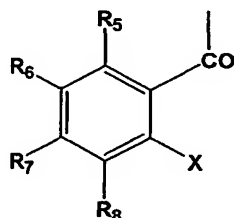
- 5 wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier. The first step is well-known strecker reaction, which is followed by conversion of cyano to acid and lastly acid to amide.

The first step involves addition of aqueous solution of sodium bisulfite in the presence of sodium cyanide in a suitable aqueous solvent. The latter two conversions are
 10 very-well documented in the literature.

Route - 5 : Compounds of general formula (II) may be prepared by the following route



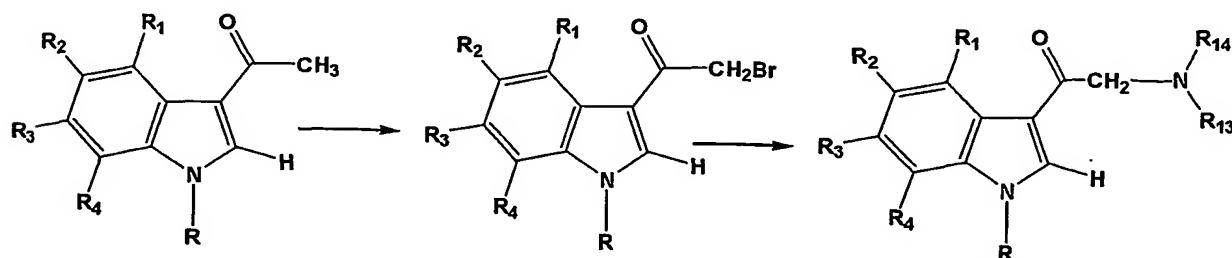
wherein R_1 , R_2 , R_3 , R_4 , R_{11} , R_{12} , R_{13} , R_{14} and n are as defined in relation to formula (I); R represents either of hydrogen or a group such as,



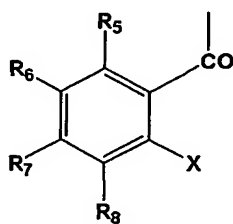
- 5 wherein X is halogen such as chloro, bromo or iodo; R_5 , R_6 , R_7 and R_8 are as defined earlier. The first step is well-known conversion of chloro to cyano, which is followed by conversion of cyano to acid and lastly acid to amide.

Route - 6 : Compounds of general formula (II) may be prepared by the following route,

10



wherein R_1 , R_2 , R_3 , R_4 , R_{11} , R_{12} , R_{13} , R_{14} and n are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

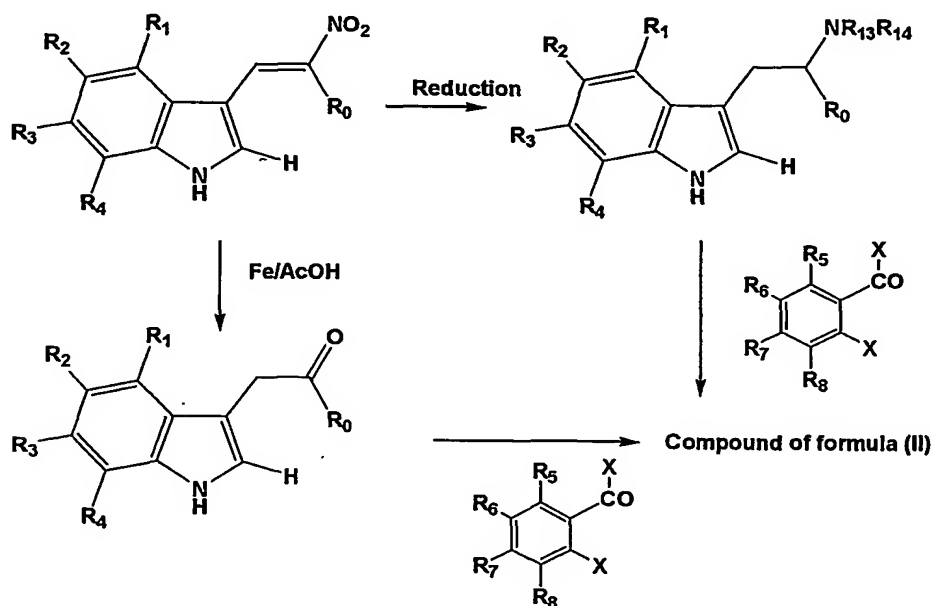


15

wherein X is halogen such as chloro, bromo or iodo; R₅, R₆, R₇ and R₈ are as defined earlier. The first step is bromination using suitable agent such as bromine, pyridinium-bromide and the like in a suitable solvent. In the next step bromine is displaced by amine according to the methods known.

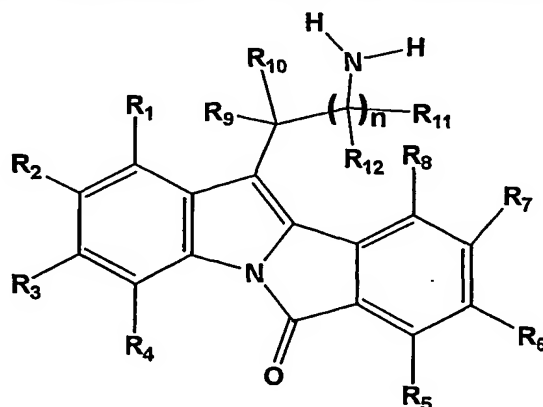
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Route - 7 : Compounds of general formula (II) may be prepared by the following route,



- 10 wherein R₁, R₂, R₃, R₄, R₁₁, R₁₂, R₁₃, R₁₄ and n (=2) are as defined above; X is halogeno
 such as chloro, bromo or iodo, R₀ is hydrogen or alkyl group. The starting material is well-
 known intermediate in indole chemistry, which upon oxidization leads to CH₂-C(=O)- type
 substitution in the side chain. Next carrying out reaction sequence as described in Route 3
 (i.e. reducing the carbonyl bond to hydroxyl) and Route 6 (i.e. bromination) differently
 15 substituted side chains can be prepared.

Novel intermediates of general formula (III) are represented as given below,

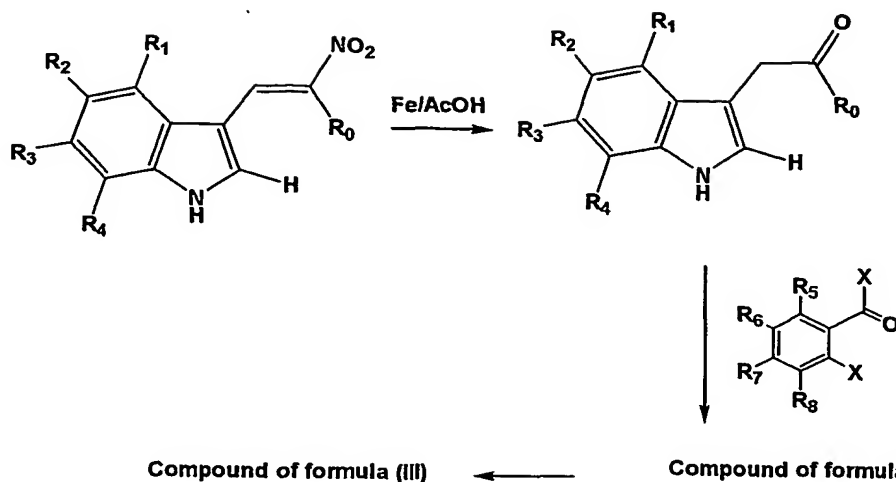


(III)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxy carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R₁ and R₂ or R₂ and R₃ or R₃ and R₄ or R₅ and R₆ or R₆ and R₇ or R₇ and R₈ together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R₉ and R₁₀ or R₁₁ and R₁₂ together represent double bond attached to "Oxygen" or "Sulfur"; or R₉ and R₁₀ or R₁₁ and R₁₂ together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined.

"n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

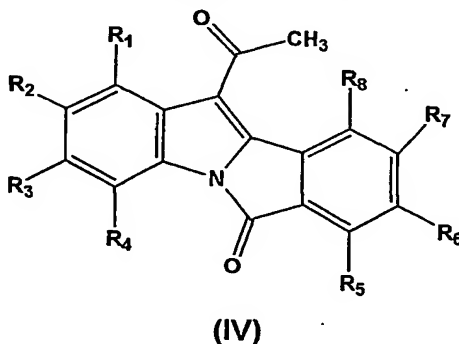
The present invention also provides a process for preparing the novel intermediate represented by the general formula (III).



Substituted indole compounds can be alkylated with 1-dimethylamino-2-nitroethylene in the presence of trifluoroacetic acid, which can be reduced with lithium aluminium hydride to give substituted tryptamines. All steps are described in J. Med. Chem., 1993, 36, 4069 and J. Med. Chem., 2000, 43, 1011-1018.

The compounds of formula (II) can be methylated through reductive alkylation using formaldehyde, sodium cyanoborohydride in acetonitrile stirring at room temperature to produce compounds of formula (I).

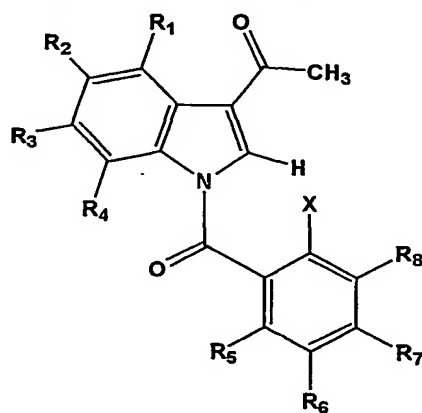
Novel intermediates of general formula (IV) are represented as given below,



wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are as may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxy carbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxy carbonylamino, aralkyloxy carbonylamino,

aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R₁ and R₂ or R₂ and R₃ or R₃ and R₄ or R₅ and R₆ or R₆ and R₇ or R₇ and R₈ together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; and R₉ and R₁₀ here represent double bond attached to "Oxygen".

The present invention also provides method to prepare intermediate by general formula (IV), which comprises of cyclizing compounds of formula (VIII),



(VIII)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are as defined above; X is halogeno such as chloro, bromo or iodo, using a Pd(0) or Pd (II) derivative as a catalyst, for example tetrakis triphenylphosphine palladium, (Bis-tri-o-tolylphosphine) palladium and the like in a suitable solvent.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, Ed J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. For example, suitable protecting groups for the piperazine group include BOC, COCCl₃, COCF₃. The protecting groups may be removed according to the standard procedures.

The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The compounds of the present invention may contain one or more asymmetric centers and therefore they also exist as stereoisomers. The stereoisomers of the

compounds of the present invention may be prepared by one or more ways presented below:

- i) One or more of the reagents may be used in their optically active form.
- ii) Optically pure catalyst or chiral ligands along with metal catalyst may be employed in the reduction process. The metal catalyst may be Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines (Principles of Asymmetric synthesis, J. E. Baldwin Ed., Tetrahedron series, 14, 311-316).
- iii) The mixture of stereoisomers may be resolved by conventional methods such as forming a diastereomeric salts with chiral acids or chiral amines, or chiral amino alcohols, chiral amino acids. The resulting mixture of diastereomers may then be separated by methods such as fractional crystallization, chromatography and the like, which is followed by an additional step of isolating the optically active product by hydrolyzing the derivative (Jacques et. al., "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981).
- iv) The mixture of stereoisomers may be resolved by conventional methods such as microbial resolution, resolving the diastereomeric salts formed with chiral acids or chiral bases.

Chiral acids that can be employed may be tartaric acid, mandelic acid, lactic acid, camphorsulfonic acid, amino acids and the like. Chiral bases that can be employed may be cinchona alkaloids, brucine or a basic amino acid such as lysine, arginine and the like.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as Lithium, ammonia, substituted ammonia, sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium t-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, dioxane, isopropanol, isopropyl ether or mixtures thereof may be used. Organic bases such lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, salicylic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, malic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, oxalic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, DMF or a lower alkyl ketone such as acetone, or the mixtures thereof.

Different polymorphs may be prepared by crystallization of compounds of general formula (I) under different conditions such as different solvents or solvent mixtures in varying proportions for recrystallization, various ways of crystallization such as slow cooling, fast cooling or a very fast cooling or a gradual cooling during crystallization. Different polymorphs may also be obtained by heating the compound, melting the compound and solidification by gradual or fast cooling, heating or melting under vacuum or under inert atmosphere and cooling under either vacuum or inert atmosphere. The various polymorphs may be identified by either one or more of the following techniques such as differential scanning calorimeter, powder X-ray diffraction, IR spectroscopy, solid probe NMR spectroscopy and thermal microscopy.

Another aspect of the present invention comprises of a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their geometric forms, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers, auxiliaries and the like.

The pharmaceutical compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parental (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or a form suitable for administration by inhalation or insufflation.

The dose of the active compounds can vary depending on factors such as the route of administration, age and weight of patient, nature and severity of the disease to be treated and similar factors. Therefore, any reference herein to a pharmacologically effective amount of the compounds of general formula (I) refers to the aforementioned factors.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol

syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges
5 formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such
10 forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions
15 such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of an aerosol spray from a pressurized container or a nebulizer, or from a capsule using an inhaler or insufflator. In the case of a
20 pressurized aerosol, a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas and the dosage unit may be determined by providing a valve to deliver a metered amount. The medicament for pressurized container or nebulizer may contain a solution or suspension of the active compound while for a capsule it preferably should be in the form of powder.
25 Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of this invention, for either oral, parenteral, nasal or buccal administration, to an average adult human, for the treatment of the
30 conditions referred to above, is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., migraine) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose
35 with an aerosol will be within the range 100 µg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The affinities of the compound of this invention for the various serotonin receptors are evaluated using standard radioligand binding assays and are described here.

Radioligand binding assays for various 5-HT receptor sub-types :

5 **i) Assay for 5HT_{1A}**

Materials and Methods:

Receptor source : Human recombinant expressed in HEK-293 cells

Radioligand : [³H]-8-OH-DPAT (221 Ci/mmol)

Final ligand concentration - [0.5 nM]

10 Reference compound : 8-OH-DPAT

Positive control : 8-OH-DPAT

Incubation conditions :

15 Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM MgSO₄, 0.5 mM EDTA and 0.1% Ascorbic acid at room temperature for 1 hour. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT_{1A} binding site.

20 Literature Reference:

• Hoyer D., Engel G., et al. Molecular Pharmacology of 5HT₁ and 5-HT₂ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [³H]-5HT, [³H]-8-OH-DPAT, [¹²⁵I]-Iodocyanopindolol, [³H]-Mesulergine and [³H]-Ketanserin. Eur. J. Pharmacol. 118: 13-23 (1985) with modifications.

25 • Schoeffter P. and Hoyer D. How Selective is GR 43175? Interactions with Functional 5-HT_{1A}, 5HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} Receptors. Naunyn-Schmiedeberg's Arch. Pharmac. 340: 135-138 (1989) with modifications.

ii) Assay for 5HT_{1B}

30 Materials and Methods:

Receptor source : Rat striatal membranes

Radioligand : [¹²⁵I]Iodocyanopindolol (2200 Ci/mmol)

Final ligand concentration - [0.15 nM]

Non-specific determinant : Serotonin - [10 μM]

35 Reference compound : Serotonin

Positive control : Serotonin

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 60 μ M (-) isoproterenol at 37°C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT_{1B} binding site.

Literature Reference:

• Hoyer D., Engel G., et al. Molecular Pharmacology of 5HT₁ and 5-HT₂ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [³H]-5HT, [³H]-8-OH-DPAT, [¹²⁵I]-Iodocyanopindolol, [³H]-Mesulergine and [³H]-Ketanserin. *Eur. J. Pharmacol.* 118: 13-23 (1985) with modifications.

• Schoeffter P. and Hoyer D. How selective is GR 43175? Interactions with Functional 5-HT_{1A}, 5HT_{1B}, 5-HT_{1C}, and 5-HT₁ Receptors. *Naunyn-Schmiedeberg's Arch. Pharmac.* 340: 135-138 (1989) with modifications.

iii) Assay for 5HT_{1D}

Materials and Methods:

Receptor source : Human cortex

Radioligand : [³H] 5-Carboxamidotryptamine (20-70 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [1.0 μ M]

Reference compound : 5-Carboxamidotryptamine (5-CT)

Positive control : 5-Carboxamidotryptamine (5-CT)

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM CaCl₂, 100 nM 8-OH-DPAT, 100 nM Mesulergine, 10 μ M Pargyline and 0.1% ascorbic acid at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the cloned 5HT_{1D} binding site.

Literature Reference:

• Waeber C., Schoeffter, Palacios J.M. and Hoyer D. Molecular Pharmacology of the 5-HT_{1D} Recognition Sites: Radioligand Binding Studies in Human, Pig, and Calf Brain

Membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. 337: 595-601 (1988) with modifications.

iv) Assay for 5HT_{2A}

5 Materials and Methods:

Receptor source : Human Cortex

Radioligand : [³H] Ketanserin (60-90 Ci/mmol)

Final ligand concentration - [2.0 nM]

Non-specific determinant : Ketanserin - [3.0 μM]

10 Reference compound : Ketanserin

Positive control : Ketanserin

Incubation conditions :

15 Reactions are carried out in 50 mM TRIS-HCl (pH 7.5) at room temperature for 90 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT_{2A} binding site.

Literature Reference:

20 • Leysen J. E., Niemegeers C. J., Van Nueten J. M. and Laduron P. M. [³H]Ketanserin: A Selective Tritiated Ligand for Serotonin₂ Receptor Binding Sites. Mol. Pharmacol. 21: 301-314 (1982) with modifications.

• Martin, G. R. and Humphrey, P. P. A. Classification Review: Receptors for 5-HT: Current Perspectives on Classification and Nomenclature. Neuropharmacol. 33(3/4): 261-
25 273 (1994).

v) Assay for 5HT_{2C}

Materials and Methods:

Receptor source : Pig choroid plexus membranes

30 Radioligand : [³H] Mesulergine (50-60 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Serotonin - [100 μM]

Reference compound : Mianserin

Positive control : Mianserin

35

Incubation conditions :

Reactions are carried out in 50 mM TRIS-HCl (pH 7.7) containing 4 mM CaCl₂ and 0.1% ascorbic acid at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT_{2C} binding site.

Literature Reference:

- A. Pazos, D. Hoyer, and J. Palacios. The Binding of Serotonergic Ligands to the Porcine Choroid Plexus: Characterization of a New Type of Serotonin Recognition Site. Eur. J. Pharmacol. 106: 539-546 (1985) with modifications.
- Hoyer, D., Engel, G., et al. Molecular Pharmacology of 5HT₁ and 5-HT₂ Recognition Sites in Rat and Pig Brain Membranes: Radioligand Binding Studies with [3H]-5HT, [3H]-8-OH-DPAT, [¹²⁵I]-Iodocyanopindolol, [3H]-Mesulergine and [3H]-Ketanserin. Eur. J. Pharmacol. 118: 13-23 (1985) with modifications.

vi) Assay for 5HT₃

Materials and Methods:

Receptor source : N1E-115 cells

Radioligand : [³H]-GR 65630 (30-70 Ci/mmol)

Final ligand concentration - [0.35 nM]

Non-specific determinant : MDL-72222 - [1.0 µM]

Reference compound : MDL-72222

Positive control : MDL-72222

Incubation conditions :

Reactions are carried out in 20 mM HEPES (pH 7.4) containing 150 mM NaCl at 25 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT₃ binding site.

Literature Reference:

- Lummis S. C. R., Kilpatrick G. J. Characterization of 5HT₃ Receptors in Intact N1E-115 Neuroblastoma Cells. Eur. J. Pharmacol. 189: 223-227 (1990) with modifications.
- Hoyer D. and Neijt H. C. Identification of Serotonin 5-HT₃ Recognition Sites in Membranes of N1E-115 Neuroblastoma Cells by Radioligand Binding. Mol. Pharmacol. 33: 303 (1988).

- Tyers M. B. 5-HT₃ Receptors and the Therapeutic Potential of 5HT₃ Receptor Antagonists. Therapie. 46:431-435 (1991).

vii) Assay for 5HT₄

5 Materials and Methods:

Receptor source : Guinea pig striatal membranes

Radioligand : [³H] GR-113808 (30-70 Ci/mmol)

Final ligand concentration - [0.2 nM]

Non-specific determinant : Serotonin (5-HT) - [30 µM]

10 Reference compound : Serotonin (5-HT)

Positive control : Serotonin (5-HT)

Incubation conditions :

15 Reactions are carried out in 50 mM HEPES (pH 7.4) at 37°C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the 5HT₄ binding site.

Literature Reference:

- 20 • Grossman Kilpatrick, C., et al. Development of a Radioligand Binding Assay for 5HT₄ Receptors in Guinea Pig and Rat Brain. Brit. J Pharmco. 109: 618-624 (1993).

viii) Assay for 5HT_{5A}

Materials and Methods:

25 Receptor source : Human recombinant expressed in HEK 293 cells

Radioligand : [³H] LSD (60-87 Ci/mmol)

Final ligand concentration - [1.0 nM]

Non-specific determinant : Methiothepin mesylate - [1.0 µM]

Reference compound : Methiothepin mesylate

30 Positive control : Methiothepin mesylate

Incubation conditions :

35 Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM MgSO₄ and 0.5 mM EDTA at 37 °C for 60 minutes. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound with the cloned 5HT_{5A} binding site.

Literature Reference:

- Rees S., et al. FEBS Letters, 355: 242-246 (1994) with modifications

5 ix) Assay for 5HT₆

Materials and Methods:

Receptor source : Human recombinant expressed in HEK293 cells

Radioligand : [³H]LSD (60-80 Ci/mmol)

Final ligand concentration - [1.5 nM]

10 Non-specific determinant : Methiothepin mesylate - [0.1 μM]

Reference compound : Methiothepin mesylate

Positive control : Methiothepin mesylate

Incubation conditions :

15 Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM MgCl₂, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin - 5HT₆ binding site.

20

Literature Reference:

- Monsma F. J. Jr., et al., Molecular Cloning and Expression of Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs. Mol. Pharmacol. (43): 320-327 (1993).

25 x) Assay for 5-HT₇

Materials and Methods:

Receptor source : Human recombinant expressed in CHO cells

Radioligand : [³H]LSD (60-80 Ci/mmol)

Final ligand concentration - [2.5 nM]

30 Non-specific determinant : 5-Carboxamidotryptamine (5-CT) - [0.1 μM]

Reference compound : 5-Carboxamidotryptamine

Positive control : 5-Carboxamidotryptamine

Incubation conditions :

35 Reactions are carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM MgCl₂, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction is terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters is determined and compared to control

values in order to ascertain any interactions of test compound(s) with the cloned serotonin - 5HT₇ binding site.

Literature Reference:

- 5 • Y. Shen, E. Monsma, M. Metcalf, P. Jose, M Hamblin, D. Sibley, Molecular Cloning and Expression of a 5-hydroxytryptamine₇ Serotonin Receptor Subtype. J. Biol. Chem. 268: 18200-18204.

10 The following description illustrates the method of preparation of variously substituted compounds of general formula (I), according to the methods described herein. These are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

Commercial reagents were utilized without further purification. Room temperature refers to 25 - 30 °C. Melting points are uncorrected. IR spectra were taken using KBr and in solid state. Unless otherwise stated, all mass spectra were carried out using ESI conditions. 15 ¹H NMR spectra were recorded at 300 MHz on a Bruker instrument. Deuterated chloroform (99.8 % D) was used as solvent. TMS was used as internal reference standard. Chemical shift values are expressed in are reported in parts per million (δ)-values. The following abbreviations are used for the multiplicity for the NMR signals: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, 20 tt=triplet of triplets, m=multiplet. NMR, mass were corrected for background peaks. Specific rotations were measured at room temperature using the sodium D (589 nm). Chromatography refers to column chromatography performed using 60 – 120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

25 **Description 1 : N,N-Dimethyl-1-(2'-bromobenzoyl)tryptamine (D1)**

A suspension of potassium hydride (15.0 mmoles, 2.0 g. (30 % suspension in mineral oil), washed with THF before use), in 30 mL of THF was stirred and cooled at 10 °C. To this cooled solution was added a solution of N,N-dimethyltryptamine (15 mmoles), in THF, slowly, over 15 min., maintaining the temperature below 10 °C. After that a solution of 2- 30 bromobenzoyl chloride in THF (15 mmoles, in 10 mL of THF) was then added under nitrogen blanket and the reaction temperature was maintained below 10 °C (Exothermic reaction). Further, the reaction mixture was maintained at 20 - 25 °C for further 2 - 4 hrs. After completion of reaction (TLC), the excess of THF was distilled off and the concentrate was diluted with ice-water and extracted with ethyl acetate. Combined ethyl acetate layer was 35 washed with water, dried over sodium sulfate and evaporated under reduced pressure, below 50 °C.

The crude residue was purified by silica gel column chromatography using 30 % methanol in ethyl acetate as a mobile phase, to obtain the intermediate, N,N-Dimethyl-1-(2'-bromobenzoyl)tryptamine, which was identified by IR, NMR and mass spectral analyses.

5 Description 2 – 21 (D2 – D21) :

Various indole intermediates were reacted with substituted 2-bromobenzoyl chloride according to the procedure described in the description 1. These compounds were identified by IR, NMR and mass spectral analyses. The following list includes list of such compounds.

10 List – 1 :

	Description	Mass ion (M+H) ⁺
D 1	2-[1-(2-Bromobenzoyl)indol3-yl]ethyl-N,N-dimethylamine	371
D 2	2-[1-(2-Bromobenzoyl)-5-bromoindol3-yl]ethyl-N,N-dimethylamine	449
D 3	2-[1-(2-Bromobenzoyl)-5-chloroindol3-yl]ethyl-N,N-dimethylamine	405
D 4	2-[1-(2-Bromobenzoyl)-5-fluoroindol3-yl]ethyl-N,N-dimethylamine	389
D 5	2-[1-(2-Bromobenzoyl)-5-methylindol3-yl]ethyl-N,N-dimethylamine	385
D 6	2-[1-(2-Bromobenzoyl)-5-methoxyindol3-yl]ethyl-N,N-dimethylamine	401
D 7	2-[1-(2-Bromobenzoyl)-7-ethylindol3-yl]ethyl-N,N-dimethylamine	399
D 8	2-[1-(2-Bromobenzoyl)-7-chloroindol3-yl]ethyl-N,N-dimethylamine	405
D 9	2-[1-(2-Bromobenzoyl)-7-methoxyindol3-yl]ethyl-N,N-dimethylamine	401
D 10	2-[1-(2-Bromobenzoyl)-7-trifluoromethylindol3-yl]ethyl-N,N-dimethylamine	439
D 11	2-[1-(2-Bromobenzoyl)-5,7-dichloroindol3-yl]ethyl-N,N-dimethylamine	439
D 12	2-[1-(2-Bromobenzoyl)-6,7-dichloroindol3-yl]ethyl-N,N-dimethylamine	439
D 13	2-[1-(2-Bromobenzoyl)-5,7-difluoroindol3-yl]ethyl-N,N-dimethylamine	407
D 14	2-[1-(2-Bromobenzoyl)-5,7-dimethylindol3-yl]ethyl-N,N-dimethylamine	399
D 15	2-[1-(2-Bromobenzoyl)-6,7-dimethylindol3-yl]ethyl-N,N-dimethylamine	399
D 16	2-[1-(2-Bromobenzoyl)-4-chloro-7-methylindol3-yl]ethyl-N,N-dimethylamine	419
D 17	2-[1-(2-Bromobenzoyl)-6-chloro-7-methylindol3-yl]ethyl-N,N-dimethylamine	419
D 18	2-[1-(2-Bromobenzoyl)-4,5,7-trichloroindol3-yl]ethyl-N,N-dimethylamine	473
D 19	2-[1-(2-Bromobenzoyl)indol3-yl]-1-hydroxyethyl-N,N-dimethylamine	387
D 20	1-(2-Bromobenzoyl)-5-bromo-3-(2-(morpholino-1-yl)ethyl)-1H-indole	491
D 21	1-(2-Bromobenzoyl)-(2-(4-methyl-piperazin-1-yl)ethyl)-1H-indole	504

Example - 1 : 11-(2-N,N-Dimethylaminoethyl)isoindolo[2,1-a]indol-6-one

1-(2'-bromobenzoyl)-N,N-dimethyltryptamine (0.286 moles) was taken in a 100 mL 3 necked round bottomed flask, along with N,N-dimethyl acetamide (40 mL), potassium acetate (0.286 moles, 0.281 g.) and dichloro bis(tri-o-tolylphosphine)palladium (0.0143 moles, 0.0126 g.). The reaction mixture was maintained under nitrogen atmosphere and was heated to 160 °C with stirring for 16 hrs. After the completion of reaction (TLC), excess of dimethyl acetamide was distilled off under reduced pressure.

The residue obtained was purified by silica gel column chromatography using 20 % methanol in ethyl acetate as an eluent, to afford the title compound, which was identified by IR, NMR and mass spectral analyses. The final desired compound of general formula (I) can be further purified by preparation of their acid addition salts. IR spectra (cm⁻¹) : 2939, 2779, 1721, 1446; Mass (m/z) : 291 (M+H)⁺; ¹H-NMR (δ ppm) : 2.38 (6H, s), 2.57 - 2.69 (2H, m), 3.00 - 3.10 (2H, m), 7.12 - 7.90 (8H, m).

Example - 2 : 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 112- 117; IR spectra (cm⁻¹) : 2940, 2780, 1730, 1466, 1446; Mass (m/z) : 309 (M+H)⁺; ¹H-NMR (δ ppm) : 2.36 (6H, s), 2.57 - 2.65 (2H, m), 2.95 - 3.00 (2H, m), 6.93 - 7.81 (7H, m).

Example - 3 : 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one hydrochloride salt

Example no. 2 (199 mg) was dissolved in 30 mL ether. To this clear solution a mixture of isopropylalcohol-hydrochloric acid (10 mL) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : >250 (dec).

Example - 4 : 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one maleic acid salt

Example no. 2 (205 mg) was dissolved in 30 mL ether. To this clear solution a solution of maleic acid (82 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 180 - 182 (dec).

Example - 5 : 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one D,L-malic acid salt

Example no. 2 (208 mg) was dissolved in 30 mL ether. To this clear solution a solution of D,L- malic acid (106 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 170 - 173.

5

Example - 6 : **11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one oxalate salt**

Example no. 2 (203 mg) was dissolved in 30 mL ether. To this clear solution a solution of oxalic acid (94 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 244 - 246 (dec).

10

Example - 7 : **11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one citrate salt**

Example no. 2 (201 mg) was dissolved in 30 mL ether. To this clear solution a solution of citric acid (134 mg, dissolved in 30 mL ether + 5 mL methanol) was added. Immediately a white precipitate separates out, which was filtered, washed with ether and dried. Melting range (°C) : 178 - 180.

15

Example - 8 : **2-Bromo-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 118 - 121; IR spectra (cm⁻¹) : 2942, 2759, 1718, 1444, 882, 761; Mass (m/z) : 369 (M+H)⁺, 371 (M+3)⁺; ¹H-NMR (δ ppm) : 2.36 (6H, s), 2.57 - 2.65 (2H, m), 2.95 - 3.00 (2H, m), 7.29 - 7.77 (7H, m).

20

25

Example - 9 : **2-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm⁻¹) : 2925, 2765, 1723, 1446, 1381, 758, 700; Mass (m/z) : 325 (M+H)⁺; ¹H-NMR (δ ppm) : 2.32 (6H, s), 2.54 - 2.62 (2H, m), 2.76 - 2.84 (2H, m), 7.27 - 7.73 (7H, m).

30

Example - 10 : **4-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one**

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm⁻¹) : 2942, 2779, 1746, 1417, 1343, 782, 700; Mass (m/z) : 325 (M+H)⁺; ¹H-NMR (δ ppm) : 2.90 (6H, s), 3.27 - 3.31 (2H, m), 3.52 - 3.57 (2H, m), 7.07 - 8.09 (7H, m).

35

Example - 11 : 11-[(2-N,N-Dimethylamino)ethyl]-2-methylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 116 - 128; IR spectra (cm⁻¹) : 2941, 2761, 1714, 1611, 1468; Mass (m/z) : 305 (M+H)⁺; ¹H-NMR (δ ppm) :
5 2.39 (6H, s), 2.42 (3H, s), 2.57 - 2.76 (2H, m), 2.99 - 3.07 (2H, m), 7.07 - 7.67 (7H, m).

Example - 12 : 11-[(2-N,N-Dimethylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm⁻¹) : 2941, 2773, 1466,
10 1371, 1237; Mass (m/z) : 321 (M+H)⁺; ¹H-NMR (δ ppm) : 2.39 (6H, s), 2.60 - 2.68 (2H, m), 2.98 - 3.06 (2H, m), 3.85 (3H, s), 6.84 - 7.66 (7H, m).

Example - 13 : 11-[(2-N,N-Dimethylamino)ethyl]-4-methoxyisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. IR spectra (cm⁻¹) : 2941, 2773, 1728,
15 1466, 1230; Mass (m/z) : 321 (M+H)⁺.

Example - 14 : 11-[(2-N,N-Dimethylamino)ethyl]-4-trifluoromethylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 359 (M+H)⁺.

Example - 15 : 11-[(2-N,N-Dimethylamino)ethyl]-4-ethylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 319 (M+H)⁺.

Example - 16 : 11-[(2-N,N-Dimethylamino)ethyl]-2,4-difluoroisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 327 (M+H)⁺.

Example - 17 : 2,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 359 (M+H)⁺.

Example - 18 : 3,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 359 (M+H)⁺.

5

Example - 19 : 1,2,4-Trichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 393 (M+H)⁺.

10

Example - 20 : 11-[(2-N,N-Dimethylamino)ethyl]-2,4-dimethylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 100 - 102; IR spectra (cm⁻¹) : 2942, 2758, 1721, 1449, 1242; Mass (m/z) : 319 (M+H)⁺; ¹H-NMR (δ ppm) : 2.36 (3H, s), 2.38 (6H, s), 2.61 - 2.65 (2H, m), 2.84 (3H, m), 2.97 - 3.00 (2H, s), 6.87 - 7.75 (6H, m).

15

Example - 21 : 11-[(2-N,N-Dimethylamino)ethyl]-3,4-dimethylisoindolo[2,1-a]indol-6-one

20

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 119 - 121; IR spectra (cm⁻¹) : 2941, 2762, 1719, 1305; Mass (m/z) : 319 (M+H)⁺; ¹H-NMR (δ ppm) : 2.35 (3H, s), 2.38 - 2.40 (6H, s), 2.61 - 2.65 (2H, m), 2.86 (3H, m), 2.98 - 3.06 (2H, s), 6.98 - 7.76 (6H, m).

25

Example - 22 : 1-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 339 (M+H)⁺.

30

Example - 23 : 3-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 339 (M+H)⁺.

35

Example - 24 : 11-[(2-N,N-Dimethylamino)propyl]-4-methylisoindolo[2,1-a]indol-6-one

Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Mass (m/z) : 305 (M+H)⁺.

Example - 25 : 2-Bromo-11-[(2-morpholin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one

5 Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 148 - 151; IR spectra (cm⁻¹) : 2956, 2806, 1733, 1438, 1360; Mass (m/z) : 411 (M+H)⁺; ¹H-NMR (δ ppm) : 2.56 - 2.63 (4H, t), 2.63 - 2.71 (2H, m), 2.98 - 3.06 (2H, m), 3.74 - 3.78 (4H, t), 7.31 - 7.79 (7H, m).

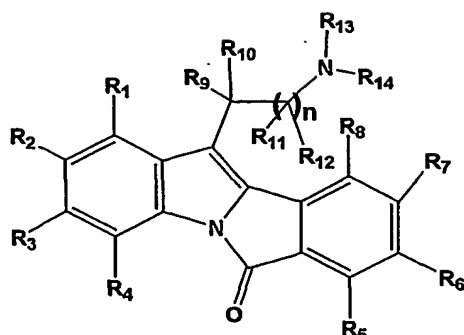
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Example - 26 : 2-Bromo-11-[2-(4-methylpiperazin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one

15 Using essentially the general procedure described in example 1 and some non-critical variations, the above derivative was prepared. Melting range (°C) : 146 - 150; IR spectra (cm⁻¹) : 2940, 2790, 1725, 1440, 1357, 801, 703; Mass (m/z) : 424 (M+H)⁺; ¹H-NMR (δ ppm) : 2.28 - 2.32 (3H, t), 2.52 - 2.75 (10H, m), 2.98 - 3.05 (2H, m), 7.30 - 7.78 (7H, m).

We Claim,

1. A compound of the general formula (I),



General Formula (I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and solvates,

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or

one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

5 R₁₃ and R₁₄ may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₂-C₁₂)alkanoyl (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R₁₃ and R₁₄ along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three
10 double bonds or "additional heteroatoms", as defined above; and
"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain.

2. A compound according to Claim -1, which is selected from the group consisting of:

- 15 11-(2-N,N-Dimethylaminoethyl)isoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one hydrochloride salt;
11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one maleic acid salt;
11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one D,L-malic acid salt;
20 11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one oxalate salt;
11-[(2-N,N-Dimethylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one citrate salt;
11-[(2-N-cyclopropyl-N-methylamino)ethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
11-[2-N-cyclopropylethyl]-2-fluoroisoindolo[2,1-a]indol-6-one;
2-Bromo-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
25 2-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
4-Chloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-2-methylisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Diacetyl amino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
30 11-[(2-N-Acetyl amino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-4-methoxyisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-4-trifluoromethylisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-4-ethylisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-2,4-difluoroisoindolo[2,1-a]indol-6-one;
35 2,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
3,4-Dichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;
1,2,4-Trichloro-11-[(2-N,N-dimethylamino)ethyl]isoindolo[2,1-a]indol-6-one;

11-[(2-N,N-Dimethylamino)ethyl]-2,4-dimethylisoindolo[2,1-a]indol-6-one;
11-[(2-N,N-Dimethylamino)ethyl]-3,4-dimethylisoindolo[2,1-a]indol-6-one;
1-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N,N-diacetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
5 3-Chloro-11-[(2-N-acetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-acetylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-acetylamino)ethyl]-2-sulfoamidoisoindolo[2,1-a]indol-6-one;
3-Iodo-11-[(2-N-acetylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N,N-dimethylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
10 11-[(2-N,N-Dimethylamino)propyl]-4-methylisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-methylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-methyl-N-acetylamino)ethyl]-4-methylisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-methylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
3-Chloro-11-[(2-N-methylamino)ethyl]-2-sulfoamidoisoindolo[2,1-a]indol-6-one;
15 3-Iodo-11-[(2-N-methylamino)ethyl]-2-methoxyisoindolo[2,1-a]indol-6-one;
2-Bromo-11-[(2-morpholin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one;
2-Bromo-11-[2-(4-methylpiperazin-1-yl)ethyl]isoindolo[2,1-a]indol-6-one;

and its stereoisomers, its N-oxides, its polymorphs, its pharmaceutically acceptable salts and solvates.

20 3. A pharmaceutical composition comprising either of a pharmaceutically acceptable carrier, diluent/s, excipient/s or solvates along with a therapeutically effective amount of a compound according to Claim-1, its derivatives, its analogs, its tautomeric forms, its stereoisomers, its geometric forms, its N-oxides, its polymorphs, its pharmaceutically acceptable salts, or solvates.

25 4. A pharmaceutical composition according to Claim-3, in the form of a tablet, capsule, powder, lozenges, suppositories, syrup, solution, suspension or injectable, administered in, as a single dose or multiple dose units.

30 5. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for preparing medicaments.

35 6. Use of compound of general formula (I), as defined in Claim-1 or a pharmaceutical composition as defined in Claim-3 for the treatment where a modulation of 5-HT and/or Melatonin activity is desired.

7. Use of a compound as claimed in Claim-1 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective action on 5-HT and/or Melatonin receptors is indicated.
- 5 8. Use of a compound as claimed in Claim-1 for the treatment and/or prevention of clinical conditions such as anxiety, depression, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal
10 from drug abuse, panic attacks, chronobiological abnormalities, circadian rhythms, anxiolytic, osteoporosis, ischemic stroke, lower the risk of SIDS in young infants with low endogenous melatonin levels, reproduction, glaucoma, sleep disorders and also disorders associated with spinal trauma and /or head injury.
- 15 9. Use of a compound as claimed in Claim-1 for the treatment of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea.
- 20 10. Use of a compound as claimed in Claim-1 for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis.
- 25 11. Use of a compound as claimed in Claim-1 to reduce morbidity and mortality associated with the excess weight.
- 30 12. Use of a radiolabelled compound as claimed in Claim-1, as a diagnostic tool for modulating 5-HT and/or melatonin receptor function.
- 35 13. Use of a compound as claimed in Claims 1 in combination with a 5-HT re-uptake inhibitor, and / or a pharmaceutically acceptable salt thereof.
14. A compound of the general formula (1), its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts and its pharmaceutically acceptable solvates for preparing a medicament.
15. A method for the treatment and/or prophylaxis of clinical conditions such as anxiety, convulsive disorders, obsessive-compulsive disorders, migraine headache, cognitive

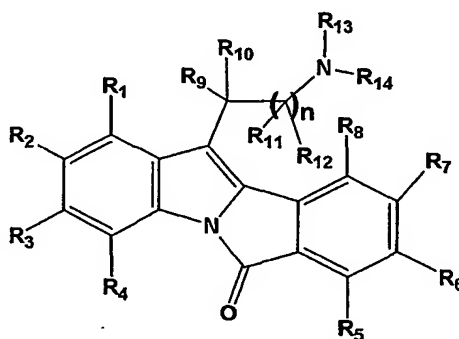
memory disorders, ADHD (Attention Deficient Disorder/ Hyperactivity Syndrome), personality disorders, psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, withdrawal from drug abuse, panic attacks, chronobiological abnormalities, circadian rhythms, anxiolytic, osteoporosis, ischemic stroke, lower the risk of SIDS in young infants with low endogenous melatonin levels, reproduction, glaucoma, sleep disorders and also disorders associated with spinal trauma and /or head injury which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

16. A method for the treatment and/or prophylaxis of mild cognitive impairment and other neurodegenerative disorders like Alzheimer's disease, Parkinsonism and Huntington's chorea which comprises administering to a patient in need thereof, an effective amount of a compound of general formula (I) as claimed in Claim-1.

17. A method for the treatment of certain GI (Gastrointestinal) disorders such as IBS (Irritable bowel syndrome) or chemotherapy induced emesis using a compound of general formula (I) as claimed in Claim-1.

18. A method to reduce morbidity and mortality associated with the excess weight using a compound of general formula (I) as claimed in Claim-1.

19. A process for the preparation of a compound of general formula (I),

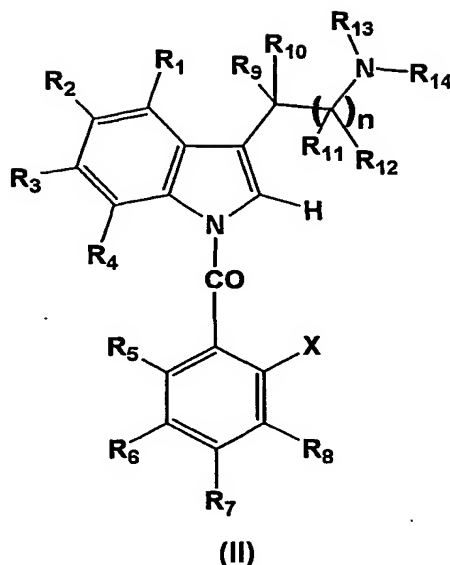


wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl,

aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxy carbonylamino, aralkyloxy carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

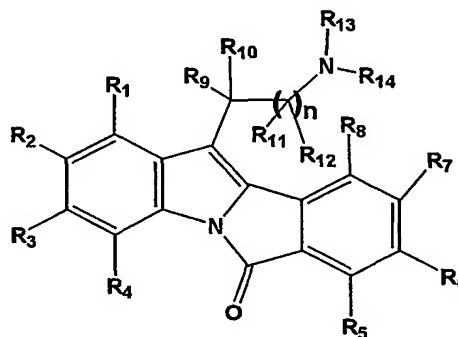
R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_2-C_{12}) alkanoyl (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of cyclizing, a compound of formula (II) given below,



wherein X is halogen such chloro, bromo or iodo, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄ and "n", wherein all the symbols are as defined above, using a Pd(0) or Pd (II) derivative as a catalyst.

20. A process for the preparation of a compound of general formula (I),

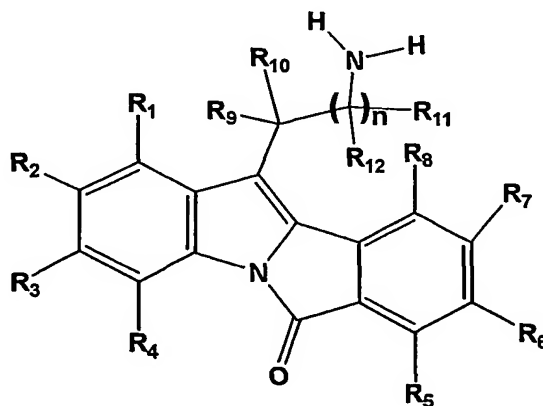


wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl,

aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxy-carbonylamino, aryloxy-carbonylamino, aralkyloxy-carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1 - C_{12})alkyl, (C_2 - C_{12})alkenyl, (C_2 - C_{12})alkynyl, (C_2 - C_{12})alkanoyl (C_3 - C_7)cycloalkyl, (C_3 - C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

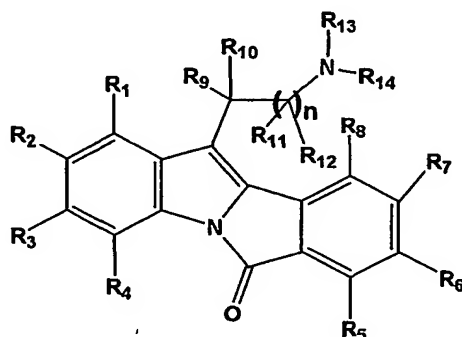
"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of reacting a compound (III) given below,



(III)

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} and "n" are as defined above, with a suitable alkylating agent such as $R_{13}X$ or $R_{14}X$ or $XR_{13}R_{14}X$ in successive steps or in one step, wherein X is good leaving group such as halogen and hydroxyl.

- 5 21. A process for the preparation of a compound of general formula (I),

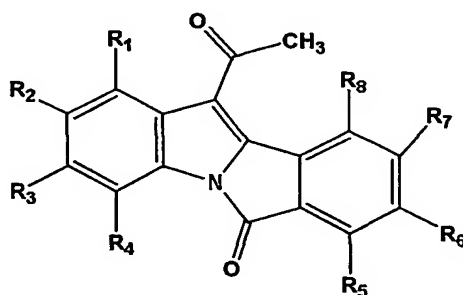


wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1-C_{12}) alkoxy, cyclo (C_3-C_7) alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxy carbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxy carbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxy carbonylamino, aralkyloxy carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R_9 and R_{10} or R_{11} and R_{12} together represent double bond attached to "Oxygen" or "Sulfur"; or R_9 and R_{10} or R_{11} and R_{12} together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or

one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined;

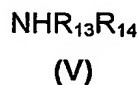
R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1 - C_{12})alkyl, (C_2 - C_{12})alkenyl, (C_2 - C_{12})alkynyl, (C_2 - C_{12})alkanoyl (C_3 - C_7)cycloalkyl, (C_3 - C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above; and

"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents may be either linear or branched carbon chain; which comprises of reacting a compound of (IV) given below,



(IV)

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are as defined above, with formaldehyde and a compound of formula (V) given below,

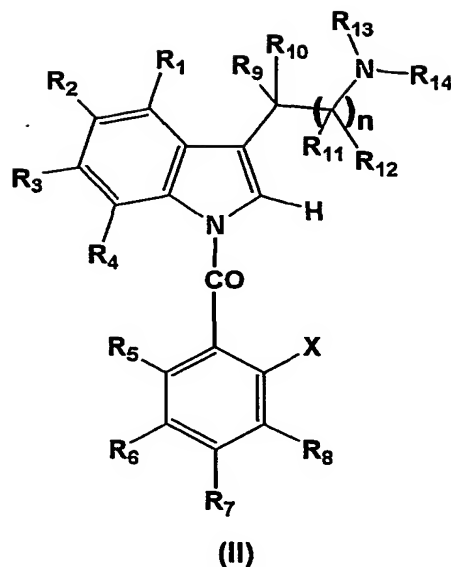


wherein R_{13} and R_{14} are as defined above.

22. A process for the preparation of compound of formula (I), which comprises of either chemically or catalytically reducing compounds containing $-C(=O)$ group/s in the side chain, to the corresponding $-C(OH,H)$ or $-C(H,H)$ compound.

23. A process according to Claim-19 to Claim-22, comprising of carrying out one or more of the following optional steps: i) removing any protecting group; ii) resolving the racemic mixture into pure enantiomers by the known methods and iii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or iv) preparing a pharmaceutically acceptable prodrug thereof.

24. Novel intermediates defined by general formula (II),



wherein X is halogen such chloro, bromo or iodo, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclylalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxylalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R₁ and R₂ or R₂ and R₃ or R₃ and R₄ or R₅ and R₆ or R₆ and R₇ or R₇ and R₈ together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R₉ and R₁₀ or R₁₁ and R₁₂ together represent double bond attached to "Oxygen" or "Sulfur"; or R₉ and R₁₀ or R₁₁ and R₁₂ together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium"

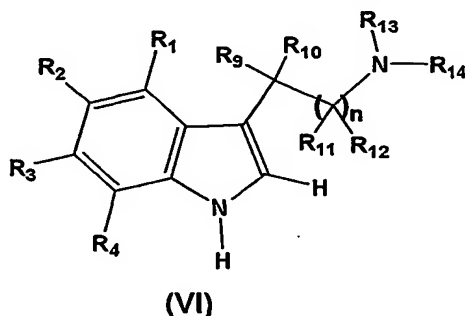
and also includes combination of one or more double bonds with "heteroatoms", as above defined;

R_{13} and R_{14} may be same or different and each independently represents hydrogen, substituted or unsubstituted groups such as linear or branched (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_2-C_{12}) alkynyl, (C_2-C_{12}) alkanoyl (C_3-C_7) cycloalkyl, (C_3-C_7) cycloalkenyl, bicycloalkyl, bicycloalkenyl, aryl, aralkyl, heteroaryl, heterocyclalkyl; optionally R_{13} and R_{14} along with the nitrogen atom, may form a 3, 4, 5, 6 or 7-membered heterocyclic ring, wherein the ring may be further substituted, and it may have either one, two or three double bonds or "additional heteroatoms", as defined above;

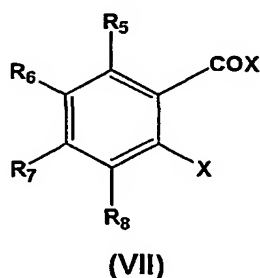
"n" is an integer ranging from 1 to 8, preferably 1 to 4, and represents either linear or branched carbon chain; and its stereoisomers and its salts.

25. A process for the preparation of novel intermediate of the general formula (II) according to any one of the routes,

Route - 1) reacting a compound of formula (VI) given below,

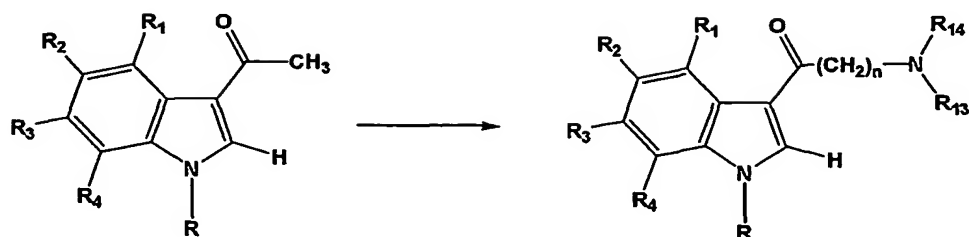


wherein R_1 , R_2 , R_3 , R_4 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} and R_{14} are as defined earlier; with a compound of formula (VII)

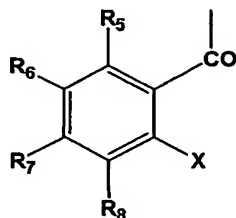


wherein R_5 , R_6 , R_7 and R_8 are as defined earlier and X is a halogeno, preferably chloro, bromo or iodo;

Route - 2) according to the following route

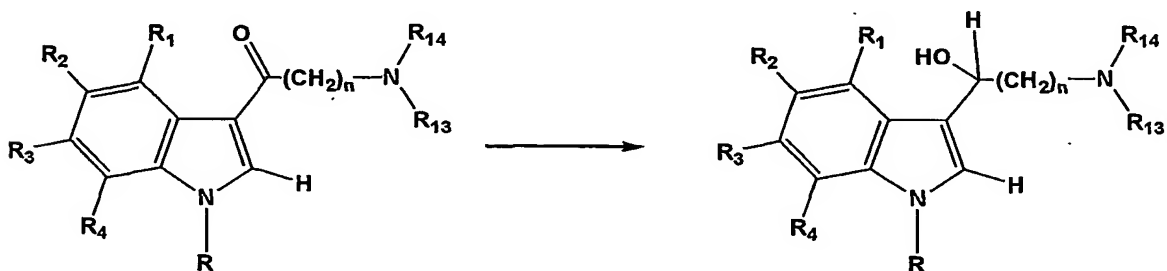


wherein R_1 , R_2 , R_3 , R_4 , R_{11} , R_{12} , R_{13} , R_{14} and n (≥ 2) are as defined earlier; R represents either of hydrogen or a group such as,

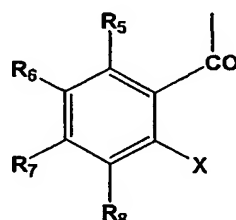


- 5 wherein X is halogen such as chloro, bromo or iodo; R_5 , R_6 , R_7 and R_8 are as defined earlier; in presence of amine hydrochloride and formaldehyde;

Route - 3) reducing another compound of formula (II) as follows,

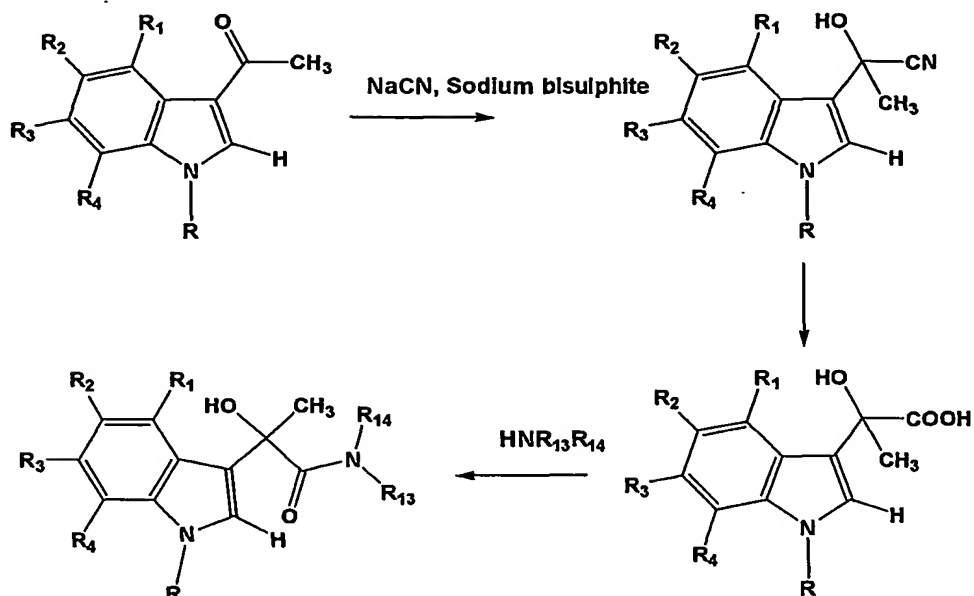


- 10 wherein R_1 , R_2 , R_3 , R_4 , R_{11} , R_{12} , R_{13} , R_{14} and n (≥ 2) are as defined earlier; R represents either of hydrogen or a group such as,

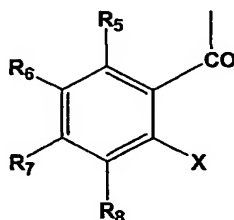


- 15 wherein X is halogen such as chloro, bromo or iodo; R_5 , R_6 , R_7 and R_8 are as defined earlier; by use of known various methods of either catalytic (for example, palladium/carbon), chemical (for example, sodium borohydride) or enzymatic reduction;

Route - 4) according to the following route,

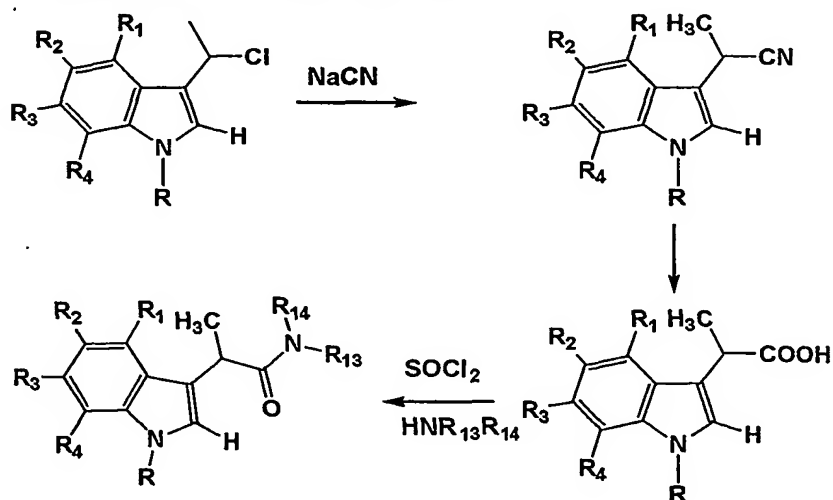


wherein $R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14}$ and n are as defined earlier; R represents either of hydrogen or a group such as,

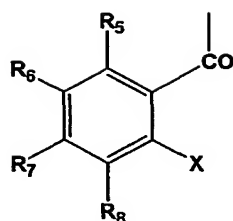


5 wherein X is halogen such as chloro, bromo or iodo; R_5, R_6, R_7 and R_8 are as defined earlier;

Route - 5) according to the following route,

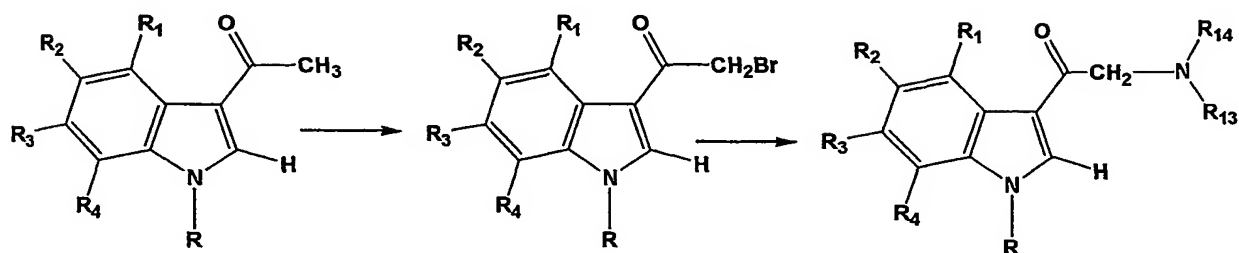


10 wherein $R_1, R_2, R_3, R_4, R_{11}, R_{12}, R_{13}, R_{14}$ and n are as defined in relation to formula (I); R represents either of hydrogen or a group such as,

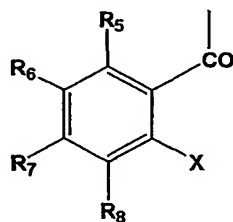


wherein X is halogen such as chloro, bromo or iodo; R₅, R₆, R₇ and R₈ are as defined earlier;

5 Route - 6) according to the following route,



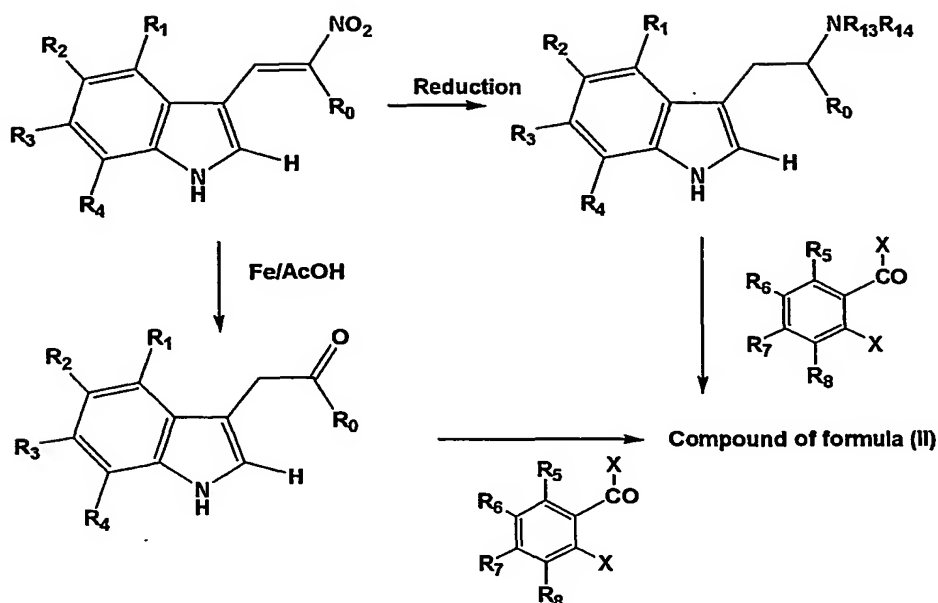
10 wherein R₁, R₂, R₃, R₄, R₁₁, R₁₂, R₁₃, R₁₄ and n are as defined earlier; R represents either of hydrogen or a group such as,



wherein X is halogen such as chloro, bromo or iodo; R₅, R₆, R₇ and R₈ are as defined earlier; and

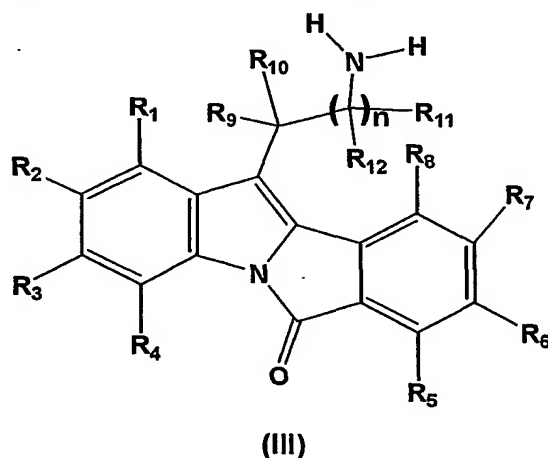
15

Route - 7) according to the following route,



wherein R_1 , R_2 , R_3 , R_4 , R_{11} , R_{12} , R_{13} , R_{14} and n ($=2$ are as defined above; X is halogen such as chloro, bromo or iodo, R_0 is hydrogen or alkyl group.

5 26. Novel intermediates of general formula (III) are represented as given below,

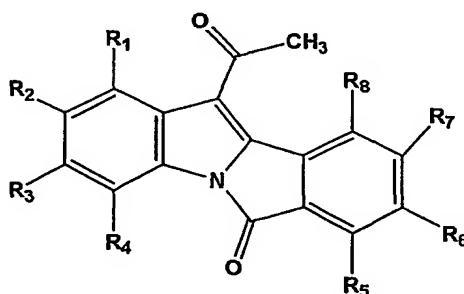


wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C_1 - C_{12})alkyl, (C_2 - C_{12})alkenyl, (C_2 - C_{12})alkynyl, (C_3 - C_7)cycloalkyl, (C_3 - C_7)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C_1 - C_{12})alkoxy, cyclo(C_3 - C_7)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclalkyloxy, acyl, acyloxy, acylamino, monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heterocyclalkoxycarbonyl, heteroaryloxycarbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl,

aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R₁ and R₂ or R₂ and R₃ or R₃ and R₄ or R₅ and R₆ or R₆ and R₇ or R₇ and R₈ together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; or R₉ and R₁₀ or R₁₁ and R₁₂ together represent double bond attached to "Oxygen" or "Sulfur"; or R₉ and R₁₀ or R₁₁ and R₁₂ together with the carbon atoms to which they are attached may form a 3, 4, 5, or 6 membered ring, which may further optionally contain one or more double bonds, and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and also includes combination of one or more double bonds with "heteroatoms", as above defined; "n" is an integer ranging from 1 to 8. It is preferred that n be 1 to 4. The carbon chains which "n" represents may be either linear or branched.

27. A process provided for the preparation of novel intermediate of the general formula (III) by cyclizing a suitable compounds of formula (II).

28. Novel intermediates defined of general formula (IV),



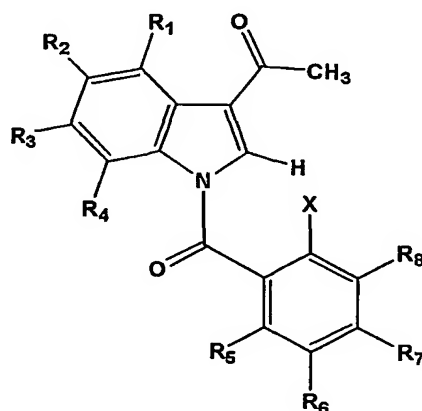
(IV)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are as may be same or different and each independently represent hydrogen, halogen, oxo, thio, perhaloalkyl, hydroxy, amino, nitro, cyano, formyl, amidino, guanidino, substituted or unsubstituted groups such as linear or branched (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkenyl, bicycloalkyl, bicycloalkenyl, (C₁-C₁₂)alkoxy, cyclo(C₃-C₇)alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclylalkyloxy, acyl, acyloxy, acylamino,

monoalkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkoxycarbonyl, aryloxy carbonyl, aralkoxy carbonyl, heterocyclalkoxy carbonyl, heteroaryloxy carbonyl, hydroxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxy carbonylamino, aralkyloxy carbonylamino, aminocarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkylamidino, alkylguanidino, dialkylguanidino, hydrazino, hydroxylamino, carboxylic acid and its derivatives, sulfonic acids and its derivatives, phosphoric acid and its derivatives; or the adjacent groups like R_1 and R_2 or R_2 and R_3 or R_3 and R_4 or R_5 and R_6 or R_6 and R_7 or R_7 and R_8 together with carbon atoms to which they are attached may form a 5, 6, or 7 membered ring, which may further optionally contain one or more double bonds and/or one or more heteroatoms such as the group "Oxygen", "Nitrogen", "Sulfur" or "Selenium" and combinations of double bond and heteroatoms; and R_9 and R_{10} here are represented as double bond attached to "Oxygen".

29. Use of compound of general formula (IV), as defined in Claim-28 for the treatment where a modulation of melatonin activity is desired.

30. A process provided for the preparation of novel intermediate of the general formula (IV) which comprises of cyclizing compounds of formula (VIII)



(VIII)

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are as defined above; X is halogeno such as chloro, bromo or iodo, using a Pd(0) or Pd (II) derivative as a catalyst.

31. Use of a compound as claimed in Claims 1 and/or Claim 28, in combination with either of 5-HT re-uptake inhibitor, Melatonin or Melatonergic modulator, and / or their pharmaceutically acceptable salts so as to achieve desired therapeutic benefit.